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EXAMINER
HUYNH, PHUONG N

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/809,753	Applicant(s) GELFAND ET AL.
	Examiner Phuong Huynh	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,12-15,20-30 and 38-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,12-15,20-30 and 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1, 3-10, 12-15, 20-30 and 38-41 are pending.

2. In view of the amendment filed 1/29/03, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3-10, 12-15, 20-30 and 38-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method to inhibit airway hyperresponsiveness in a mammal comprising administering to a mammal a calcitonin gene related peptide (CGRP) that binds to and activates a calcitonin gene related peptide (CGRP) receptor in the lungs of said mammals, wherein said mammal has or is at risk of developing, airway hyperresponsiveness, **does not** reasonably provide enablement for (1) a method to inhibit airway hyperresponsiveness in a mammal comprising administering to a mammal *any* agent such as *any* fragment of any CGRP, *any* CGRP homologue, *any* CGRP analog, any CGRP analog as a product of rational drug design that binds and activates any CGRP receptor in the lungs of said mammals, wherein said mammal has or is at risk of developing, airway hyperresponsiveness, (2) a method to inhibit airway hyperresponsiveness in a mammal comprising administering to a mammal any agent such as *any* fragment of any CGRP, *any* CGRP homologue, *any* CGRP analog, any CGRP analog as a product of rational drug design that binds and activates any CGRP receptor mentioned above in conjunction with *any* CGRP receptor activity modifying protein (RAMP) that binds and activates any CGRP receptor in the lungs of said mammals, wherein said mammal has or is at risk of developing, airway hyperresponsiveness, (3) the said method wherein the airway hyperresponsiveness is allergen-induced airway hyperresponsiveness, (4) the said method wherein said mammal has been sensitized to an allergen and has been exposed to or is at risk of being exposed to, an amount of said allergen that is sufficient to induce airway hyperresponsiveness (AHR) in said mammal in the absence of any agent mentioned above, (5) the said method further comprises monitoring said mammal to detect whether AHR in said mammal is inhibited, wherein if AHR is detected in said mammal, additional amounts of any

agent mentioned above are administered until AHR is not detected in said mammal. (6) the said method wherein said agent is administered within a time period between 48 hours or less prior to exposure to an AHR provoking stimulus that is sufficient to induce AHR and within 48 hours or less after the detection of the first symptoms of AHR. (7) the said method wherein said agent is *any* fragment of any CGRP, *any* CGRP homologue, *any* CGRP analog, *any* CGRP analog as a product of rational drug design is administered upon the detection of the first symptoms of AHR, or within 1 hours, 12 hours, or within 2 hours or less prior to exposure to a AHR provoking stimulus that is sufficient to induce AHR. (8) the said method wherein said agent is *any* fragment of any CGRP, *any* CGRP homologue, *any* CGRP analog, *any* CGRP analog as a product of rational drug design is administered to said mammals every one to two days. (9) the said method wherein said agent is *any* fragment of any CGRP, *any* CGRP homologue, *any* CGRP analog, *any* CGRP analog as a product of rational drug design is administered at a dose from about 0.1μg per kilogram, and about 20 μg per kilogram body weight of said mammal, or at a dose from about 0.1μg per kilogram, and about 10 μg per kilogram body weight of said mammal, or at a dose from about 0.1μg per kilogram, and about 5 μg per kilogram body weight of said mammal. (10) the said method wherein said agent is *any* fragment of any CGRP, *any* CGRP homologue, *any* CGRP analog, *any* CGRP analog as a product of rational drug design that binds and activates *any* CGRP receptor is targeted to cells in the lung of said mammals selected from the group consisting of smooth muscle cells and epithelial cells. (11) the said method wherein said agent is *any* fragment of any CGRP, *any* CGRP homologue, *any* CGRP analog, *any* CGRP analog as a product of rational drug design that binds and activates any CGRP receptor is administered by direct delivery of said agent to the lung by aerosol delivery or by parenteral delivery or by oral delivery. (12) the said method wherein administration of any agent such as *any* fragment of any CGRP, *any* CGRP homologue, *any* CGRP analog, *any* CGRP analog as a product of rational drug design that binds and activates any CGRP receptor reduces the airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5%. (13) the said method wherein said agent such as *any* fragment of any CGRP, *any* CGRP homologue, *any* CGRP analog, *any* CGRP analog as a product of rational drug design that binds and activates *any* CGRP receptor is administered to said mammal in conjunction with another agent such as corticosteroids (oral, inhaled and injected), β-agonist (long or short acting), leukotriene modifiers (inhibitors or receptor antagonists), antihistamines, phosphodiesterase inhibitors, sodium cromoglycate, nedocrimal and theophylline. (14) the said method wherein said agent such as *any*

fragment of any CGRP, *any* CGRP homologue, *any* CGRP analog, *any* CGRP analog as a product of rational drug design that binds and activates any CGRP receptor is administered in a pharmaceutically acceptable excipient, and (15) the said method wherein said mammal is a human for allergen induced airway hyperresponsiveness. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method to inhibit airway hyperresponsiveness (AHR) in mice sensitized to ovalbumin using only αCGRP protein. The inhibition of AHR can be block by a specific CGRP peptide (8-37 residues of the full-length αCGRP protein), which is a CGRP receptor antagonist. The specification defines the term "CGRP receptor agonist" on page 25 as any compound, any agent, including but not limited to antibody, CGRP homologue, any suitable product of drug design such as mimetic of CGRP. The specification on page 28, line 12-13, defines a CGRP protein includes protein homologues or mimetic of CGRP; the term "homologue" is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but limited to methylation, glycosylation, phosphorylation…addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification).

The specification does not teach how to make and use *any* fragment of CGRP that binds and activates any CGRP receptor, *any* CGRP homologue that binds and activates any CGRP receptor, *any* CGRP analog that binds and activates any CGRP receptor, *any* product of rational drug design that binds and activates any CGRP receptor for a method to inhibit airway hyperresponsiveness in a mammal induced by allergen. There term "fragment" could be as little as one amino acid, there is insufficient guidance as how to make any CGRP fragment that binds and activate CGRP receptor given that there are more than one CGRP receptor in the lung tissue

for a method to inhibit airway hyperresponsiveness induced by allergen in a mammal. Further, there is no guidance as to which amino acid residues within the full-length CGRP could be deleted, substituted, or added such that the resulting CGRP peptide analog would maintain both structure and function as the full length CGRP, in turn, useful for inhibiting airway hyperresponsiveness. Other than αCGRP, there are no working examples demonstrating that any agent, any fragment, any homologue, and any analog of CGRP such as products of rational drug design mentioned above that binds and activates CGRP receptor, in turn, could be use for a method to inhibit airway hyperresponsiveness.

Zhu *et al* (PTO 1449) teach calcitonin gene-related peptide (CGRP) may play different physiological and pathophysiological roles in airway regulation in different species such as horse, human Sprague-Dawley rat, and mouse (See Discussion, in particular).

Given the indefinite number of undisclosed agent such as CGRP fragment, CGRP homologue, CGRP analog and analog such as product of rational drug design that may play different physiological and pathophysiological roles in airway regulation in different species, it is unpredictable which undisclosed agent would be useful for inhibiting airway hyperresponsiveness.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 1/29/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claims have been limited to CGRP peptides fragments hereof that bind to and activate the CGRP receptor, homologues thereof that binds to and activate the CGRP receptor and analogs thereof that bind to and activate the CGRP receptor. (2) Applicants noted that the CGRP peptides is a small peptide of only 37 amino acids and that both the alpha and beta isoforms have been isolated and fully characterized. (3) Production of fragments of a 37 amino acid peptide is well within the ability of those of skill in the art and the

specification teaches how to test the biological activity of the peptide or fragment. (4) at the time of the invention, the art had already taught how to produce homologues and analogs of CGFP with biological activity. (5) Applicants have demonstrated that CGRP effectively inhibits and prevents airway hyperresponsiveness in an art-accepted model of allergic airway hyperresponsiveness and the use of the art accepted model of allergen-induced AHR in the present specification is sufficient to demonstrate a role for the administration of CGRP is sufficient to demonstrate to one skill in the art the predictability of the claimed invention.

In response to Applicants' argument to item 1, amended claims and newly added claims still recite CGRP peptides fragments, homologues thereof and analogs thereof that bind to and activate the CGRP receptor. The specification defines the term "CGRP receptor agonist" on page 25 as any compound, any agent, including but not limited to antibody, CGRP homologue, any suitable product of drug design such as mimetic of CGRP. The specification on page 28, line 12-13, defines a CGRP protein includes protein homologues or mimetic of CGRP; the term "homologue" is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification). The specification defines the term "agent can include, but is not limited to, CGRP, a fragment of CGRP that binds to and activates a CGRP receptor, and a homologue of that binds to and activates a CGRP receptor, agent produced by rational drug design that binds and activates a CGRP receptor, antibody that selectively binds to and activates the CGRP receptor". The specification discloses only a method to inhibit airway hyperresponsiveness (AHR) in mice sensitized to ovalbumin using only αCGRP protein. The inhibition of AHR can be block by a specific CGRP peptide (8-37 residues of the full-length αCGRP protein), which is a CGRP receptor antagonist.

In response to Applicants' argument to item 2, although the CGRP peptides is a small peptide of only 37 amino acids and that both the alpha and beta isoforms have been isolated and fully characterized, the agent such as any fragment of CGRP, any homologue, any agent produced by rational drug design, any mimetic of CGRP, any analogs thereof for the claimed method for inhibiting allergen-induced airway hypersensitivity in a mammal has not been fully characterized. In fact, Zhu *et al* (PTO 1449) teach calcitonin gene-related peptide (CGRP) may play different physiological and pathophysiological roles in airway regulation in different species such as horse, human Sprague-Dawley rat, and mouse (See Discussion, in particular). Even if the

CGRP is limited to the alpha CGRP protein, there is more than one CGRP receptor. Given the indefinite number of undisclosed agent, fragment of CGRP, homologue of CGRP, and product of rational drug design that may play different physiological and pathophysiological roles in airway regulation in different species, it is unpredictable which undisclosed agent would be useful for the claimed method of inhibiting allergen-induced airway hyperresponsiveness.

In response to Applicants' argument to items 2-5, although the production of fragments of a 37 amino acid peptide is well within the ability of those of skill, the issue here is not whether the fragment can be made but whether which specific fragment of CGRP, which homologue thereof, which agent produced by rational drug design, which mimetic of CGRP, and which analogs thereof bind to which CGRP receptor is effective for the claimed method of inhibiting allergen-induced airway hyperresponsiveness in any mammal using any undisclosed agent such as fragment of CGRP, homologue thereof, and analogue thereof. The specification merely alludes to the fragment of CGRP, homologue of CGRP, CGRP analog for the claimed method and does not provide the specific structure associated with said fragment of CGRP, homologue of CGRP, and CGRP analog that binds and activates a calcitonin gene related peptide CGRP receptor. In the absence of guidance as to the structure of any fragment of CGRP (i.e. amino acid residue), homologue of CGRP, and CGRP analog thereof, one skill in the art cannot make, much less how to use which undisclosed agent for the claimed method. Even at the time of the invention, the art had already taught how to produce some homologues and analogs of CGFP with biological activity, note none of the biological activity is related to the claimed method in the enclosed WO98/03686 submitted by Applicants. Further, Zhu *et al* (PTO 1449) teach calcitonin gene-related peptide (CGRP) may play different physiological and pathophysiological roles in airway regulation in different species such as horse, human Sprague-Dawley rat, and mouse (See Discussion, in particular). Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. binds to and activate CGRP receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects of the

CGRP analog, homolog and derivatives and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would lead to binding and activating the CGRP receptor derivatives and that the relationship between the sequence of a peptide, homologue, analog and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.), it would take undue amount of experimentation for one skilled in the art to practice the claimed invention even though the specification teaches how to test the biological activity of the peptide or fragment. The experimentation left to those skilled in the art is unnecessarily, improperly, extensive and undue. "A patent is not a hunting license. It is a reward for the research, but compensation for its successful conclusion" (See Brenner v. Manson).

5. Claims 1, 3-10, 12-15, 20-30 and 38-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for a method to inhibit airway hyperresponsiveness in a mammal comprising administering to a mammal *any* agent such as *any* fragment of CGRP, *any* CGRP homologue, *any* CGRP analog, *any* analog such as a product of rational drug design that binds and activates *any* CGRP receptor in the lungs of said mammals, wherein said mammal has or is at risk of developing, airway hyperresponsiveness. (2) a method to inhibit airway hyperresponsiveness in a mammal comprising administering to a mammal *any* agent such as *any* fragment of CGRP, *any* CGRP homologue, *any* CGRP analog, *any* analog such as a product of rational drug design that binds and activates *any* CGRP receptor mentioned above in conjunction with *any* CGRP receptor activity modifying protein (RAMP) that binds and activates CGRP receptor in the lungs of said mammals, wherein said mammal has or is at risk of developing, airway hyperresponsiveness.

The specification discloses only a method to inhibit airway hyperresponsiveness (AHR) in mice sensitized to ovalbumin using only αCGRP protein. The inhibition of AHR can be block by a specific CGRP peptide (8-37 residues of the full-length αCGRP protein), which is a CGRP receptor antagonist. The specification defines the term "CGRP receptor agonist" on page 25 as any compound, any agent, including but not limited to antibody, CGRP homologue, any suitable product of drug design such as mimetic of CGRP. The specification on page 28, line 12-13, defines a CGRP protein includes protein homologues or mimetic of CGRP; the term "homologue" is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification).

With the exception of the specific αCGRP mentioned above for a method of inhibiting airway hyperresponsiveness which can be reverse by CGRP peptide antagonist, there is insufficient written description about the structure associated with function of *any* fragment of CGRP, *any* homolog of CGRP, *any* analog and *any* product of rational drug design that binds and activates any CGRP receptor in conjunction with or without *any* CGRP receptor activity modifying protein (RAMP) for a method of inhibiting airway hyperresponsiveness. The term "fragment" could be as little as one amino acid without the specified amino acid sequence. The term "analog", "homologue" and *any* "product of rational drug design" without biochemical information such as amino acid sequence, or nucleotide sequence has no structure, much less binds and activates any CGRP receptor for the claimed method. The specification discloses only one specific αCGRP for the claimed method and given the lack of a written description of *any* additional representative species of fragment of CGRP, homolog of CGRP, CGRP analog or product of rational drug design that binds and activates a specific CGRP receptor for a method of inhibiting airway hyperresponsiveness, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 1/29/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claims have been limited to CGRP peptides fragments hereof that bind to and activate the CGRP receptor, homologues thereof that binds to and activate the CGRP receptor and analogs thereof that bind to and activate the CGRP receptor. (2) Applicants noted that the CGRP peptides is a small peptide of only 37 amino acids and that both the alpha and beta isoforms have been isolated and fully characterized. (3) Production of fragments of a 37 amino acid peptide is well within the ability of those of skill in the art and the specification teaches how to test the biological activity of the peptide or fragment. (4) at the time of the invention, the art had already taught how to produce homologues and analogs of CGFP with biological activity. (5) Applicants have demonstrated that CGRP effectively inhibits and prevents airway hyperresponsiveness in an art-accepted model of allergic airway hyperresponsiveness and the use of the art accepted model of allergen-induced AHR in the present specification is sufficient to demonstrate a role for the administration of CGRP is sufficient to demonstrate to one skill in the art the predictability of the claimed invention.

In response to Applicants' arguments, amended claims and newly added claims still recite CGRP peptides fragments, homologues thereof and analogs thereof that bind to and activate any CGRP receptor. The specification merely alludes to the fragment of CGRP, homologue of CGRP, CGRP analog for the claimed method and does not provide the specific structure associated with said fragment of CGRP, homologue of CGRP, and CGRP analog that binds and activates a calcitonin gene related peptide CGRP receptor. With the exception of the specific αCGRP mentioned above for a method of inhibiting airway hyperresponsiveness which can be reverse by the CGRP peptide antagonist, there is insufficient written description about the structure associated with function of *any* fragment of CGRP, *any* homologue of CGRP, *any* analog and *any* product of rational drug design that binds and activates any CGRP receptor in conjunction with or without *any* CGRP receptor activity modifying protein (RAMP) for a method of inhibiting airway hyperresponsiveness. The term "fragment" could be as little as one amino acid without the specified amino acid sequence. The term "analog", "homologue" and *any* "product of rational drug design" without biochemical information such as amino acid sequence, or nucleotide sequence has no structure, much less binds to and activates any CGRP receptor for the claimed method. The specification discloses only one specific αCGRP for the claimed method and given the lack of a written description of *any* additional representative species of

fragment of CGRP, homologue of CGRP, CGRP analog or product of rational drug design that binds and activates a specific CGRP receptor for a method of inhibiting airway hyperresponsiveness, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

6. The following new grounds of rejection are necessitated by the amendment filed 1/29/03.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 3-5, 8-9, 20, 23, 26, 29 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase *et al* (of record, Am J Respir Crit Care Med 154: 1551-56, 1996; PTO 1449) in view of Hoshino *et al* (Arcugi 38(4): 314-25, 1989, Abstract, PTO 892) or Elwood *et al* (J Allergy Clin Immunol 88(6): 951-60, 1991; PTO 892).

Nagase *et al* teach a method of inhibiting hyperpnea (dry air) induced airway hyperresponsiveness (AHR) in a mammal such as Guinea pig comprising administering to said Guinea pig an agent such as Calcitonin Gene-related peptide (CGRP) that binds to and activates a calcitonin gene related peptide receptor in the lungs (See page 1554, column 1, page 154, column 2, Effects of CGRP (8-37). The physiology of airway constriction or airway hyperresponsiveness

(AHR) in hyperpnea induced AHR is equivalent to exercise induced asthma in humans (See page 1551, column 1, in particular). Nagase *et al* teach that CGRP also inhibits leukotriene release and edema promoting actions of inflammatory mediators in several species (See page 1551, paragraph bridging column 1 and 2, in particular). Nagase *et al* teach that pretreatment with CGRP reduces HC induced airway hyperresponsiveness (AHR) in a mammal (See Fig 2, in particular). Nagase *et al* further teach pretreatment with CGRP reduced leukotriene (LTD1 induced constriction associated with asthma (See page 1555, column 2, first full paragraph, Fig 6, in particular). Nagase *et al* further teach a CGRP peptide (8-37) is a CGRP antagonist that can block the effect of Calcitonin Gene-related peptide (CGRP) (See page 154, column 2, Effects of CGRP (8-37) and CGRP on Methacholine and Endothelin-1 induced constriction, Figs 2-3, in particular). The reference method further comprises monitoring the animal to detect whether AHR is inhibited (See Methods, in particular). The reference agent is administered two minutes, which is between 48 hours or less, prior to exposure to an AHR provoking stimulus such as hyperpnea challenge or methacholine (See page 135, column 1, Effects of CGRP (8-37) and CGRP on hyperpnea induced constriction, in particular). Claims 8-9 are included in this rejection because the reference teaches administering CGRP two minutes prior to exposure to methacholine, and two minutes is within 12 hours, 2 hours or less prior to exposure to methacholine. Nagase *et al* teach administering Calcitonin Gene-related peptide (CGRP) at a dose about 0.05, 0.1, or .2 mg/kg or CGRP peptide (8-37) at a dose of ranging from 0.1, 0.2, or 0.4 mg/kg body weight of the animal (See page 154, Method in particular). The reference Calcitonin Gene-related peptide (CGRP) and CGRP peptide (8-37) target the cells in the lung such as smooth muscle cell that plays a role in airway constriction and epithelial cells (See Fig 6, in particular). The reference Calcitonin Gene-related peptide (CGRP) or CGRP peptide (8-37) is administered by injection (perenteral) in a pharmaceutically acceptable excipient such as saline (See page 154, column 1, Methods, in particular).

The claimed invention in claim 1 differs from the teachings of the reference only that the method inhibits allergen-induced airway hyperresposiveness in a mammal comprises administering to a mammal an agent such as calcitonin gene related peptide (CGRP) that binds to and activates the CGRP receptor.

Hoshino *et al* teach that allergen induced bronchoconstriction in airway in guinea sensitized to allergen such as ovalbumin (OA) is accompanied by airway hyperresponsiveness

and infiltration into the airway lumen of inflammatory cells such as eosinophils and neutrophils in bronchoalveolar lavage fluid (BALF) (See abstract, in particular).

Elwood *et al* teach that bronchial hyperresponsiveness and increase in eosinophils counts in bronchoalveolar lavage fluid (BALF) of Brown-Norway rats sensitized to allergen such as ovalbumin has many characteristics of human allergen-induced bronchial hyperresponsiveness (See abstract, in particular). Elwood *et al* teach allergen-induced bronchial responsiveness can be measured by inhaled acetylcholine challenged and animals repeatedly exposed to allergen OV had an increased baseline lung resistance which is a significant increase in bronchial responsiveness to inhaled Ach (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use CGRP to treat bronchial hyperresponsiveness such as airway constriction as taught by Nagase *et al* for the bronchoconstriction associated with allergen induced airway hyperresponsiveness as taught by Hoshino *et al* or Elwood *et al* to solve the common problem of airway constriction associated with hyperpnea induced asthma, or allergen induced asthma or leukotriene induced airway constriction. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Nagase *et al* teach that CGRP pretreatment reduces HC induced airway hyperresponsiveness (AHR) in a mammal (See Fig 2, in particular) and leukotriene (LTD1 induced airway constriction associated with asthma (See page 1555, column 2, first full paragraph, Fig 6, in particular). Hoshino *et al* teach that allergen induced bronchoconstriction in airway in guinea sensitized to allergen such as ovalbumin (OA) is accompanied by airway hyperresponsiveness and infiltration into the airway lumen of inflammatory cells such as eosinophils and neutrophils in bronchoalveolar lavage fluid (BALF) (See abstract, in particular). Elwood *et al* teach that bronchial hyperresponsiveness and increase in eosinophils counts in bronchoalveolar lavage fluid (BALF) of Brown-Norway rats sensitized to allergen such as ovalbumin has many characteristics of human allergen-induced bronchial hyperresponsiveness (See abstract, in particular).

Applicants' arguments filed 1/29/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 1 has been amended. (2) Hagase et al teach hyperpnea induced AHR and has different cause and general pathophysiology than allergen-

induced AHR. (3) Nagase et al teach administering methacholine alone as an inducer of constriction in the absence of any allergen sensitization. (4) Nagase et al saw no effect on airway constriction from the administration of CGRP.

In response to Applicants' argument, Hoshino *et al* teach that allergen induced bronchoconstriction in airway in guinea sensitized to allergen such as ovalbumin (OA) is accompanied by airway hyperresponsiveness and infiltration into the airway lumen of inflammatory cells such as eosinophils and neutrophils in bronchoalveolar lavage fluid (BALF) (See abstract, in particular). Elwood *et al* teach that bronchial hyperresponsiveness and increase in eosinophils counts in bronchoalveolar lavage fluid (BALF) of Brown-Norway rats sensitized to allergen such as ovalbumin has many characteristics of human allergen-induced bronchial hyperresponsiveness (See abstract, in particular). Elwood *et al* further teach bronchial hyperresponsiveness and increase in eosinophils counts in bronchoalveolar lavage fluid (BALF) of Brown-Norway rats sensitized to allergen such as ovalbumin has many characteristics of human allergen-induced bronchial hyperresponsiveness (See abstract, in particular).

Nagase *et al* teach a method of inhibiting hyperpnea (dry air) induced airway hyperresponsiveness (AHR) in a mammal such as Guinea pig comprising administering to said Guinea pig an agent such as Calcitonin Gene-related peptide (CGRP) that binds to and activates a calcitonin gene related peptide receptor in the lungs (See page 1554, column 1, page 154, column 2, Effects of CGRP (8-37). The physiology of airway constriction or airway hyperresponsiveness (AHR) in hyperpnea induced AHR is equivalent to exercise induced asthma in humans (See page 1551, column 1, in particular) or allergen induced airway constriction associated with airway hyperresponsiveness (AHR) as taught by the Hoshino *et al.* Nagase et al teach that pretreatment with CGRP reduced HC induces airway hyperresponsiveness (AHR) in a mammal (See Fig 2, in particular). Nagase et al further teach pretreatment with CGRP reduces leukotriene (LTD1) induced constriction and LTD1 is associated with allergen-induced asthma (See page 1555, column 2, first full paragraph, Fig 6, in particular). The combined teachings particularly Nagase *et al*, Hoshino *et al* and Elwood *et al* provide clear direction, motivation and expectation of success in treating airway bronchoconstriction using CGRP.

10. Claims 1, 3-10, 21-24, 27, 29-30 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase *et al* (of record, Am J Respir Crit Care Med 154: 1551-56, 1996; PTO 1449) in view of Hoshino et al (Areugi 38(4): 314-25, 1989, Abstract, PTO 892), Elwood et al (J Allergy Clin Immunol 88(6): 951-60, 1991; PTO 892) and US Pat No. 5,858,978 (of record, Jan 1999; PTO 1449) or US Pat No. 5,635,478 (of record, June 1997; PTO 1449).

The teachings of Nagase *et al*, Hoshino *et al* and Elwood *et al* have been discussed supra.

The claimed invention in claim 1 differs from the teachings of the combined references only that the method inhibits allergen-induced airway hyperresponsiveness in a mammal comprises administering to a mammal an agent such as calcitonin gene related peptide (CGRP) that binds to and activates the CGRP receptor.

The claimed invention in claim 6 differs from the teachings of the combined references only that the method wherein the agent is administered upon the detection of the first symptoms of AHR.

The claimed invention in claim 7 differs from the teachings of the references only that the method wherein the agent is administered within one hour after the detection of the first symptoms of AHR.

The claimed invention in claim 10 differs from the teachings of the combined references only that the method wherein the agent is administered every one to two days.

The claimed invention in claim 21 differs from the teachings of the combined teachings of the references only that the method wherein the agent is administered by directly delivers to the lung of said mammal.

The claimed invention in claim 22 differs from the teachings of the combined references only that the method wherein the agent is administered by aerosol delivery.

The claimed invention in claim 24 differs from the teachings of the combined references only that the method wherein the agent is administered by oral delivery.

The claimed invention in claim 27 differs from the teachings of the combined references only that the method wherein the agent is administered to said mammal in conjunction with another agent such as corticosteroids (oral or injected), or phosphodiesterase inhibitor.

The claimed invention in claim 30 differs from the teachings of the combined references only that the method wherein the mammal is a human.

The claimed invention in claim 40 differs from the teachings of the combined references only that the method wherein the agent is a homologue of CGRP that binds and activates a CGRP receptor.

The '978 patent teaches a method of using agent such as calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat for a method of inhibiting acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness due to constriction, in human (See column 5, lines 12-13, column 7, lines 45-49, claims of '978 patent, in particular). The reference agents are administered into the respiratory tract such as the lung by aerosol spray (See column 7, lines 45-49, in particular) or administered orally such as tablet or sublingual (See column 6, lines 3-7, in particular). The '978 patent teaches the reference method is useful in treatment of a variety of acute and chronic inflammatory respiratory disorders by administering CGRP alone and in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor conventionally used to treat such diseases (See column 5, lines 36-39, lines 47-53, in particular). The '978 patent teaches the pharmaceutical composition comprises an effective unit dosage at a concentration effective to evoke the desired response by the route appropriate for the particular pharmaceutical carrier (See column 7, lines 6-61, in particular). The '978 patent teaches that the reference agents are administered in multiple successive dosages, spaced as frequently as 6-12 hours apart or as long as six weeks until symptomatic relief is obtained (See column 7, lines 50-55, in particular) or every 24 hours or longer (See column 7, lines 35, in particular).

The '478 patent teaches a method of using agent such as calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat for a method of inhibiting acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness in human (See column 13, lines 1-6, column 2, lines 39-66 column 3, lines 1-8, in particular). The reference agents are administered into the respiratory tract such as the lung by aerosol spray (See column 6, lines 35, in particular) or administered orally (See column 7, line 3, in particular) or administered by parenterally (See column 6, lines 37-38, in particular). The '478 patent teaches the reference agents are useful in treatment of a variety of acute and chronic inflammatory respiratory disorders, by administering CGRP alone or in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor which conventionally used to treat such diseases (See column 5, lines 36-39, lines 47-53, in particular). The '478 patent teaches the pharmaceutical composition comprises an effective

unit dosage at a concentration effective to evoke the desired response by the route appropriate for the particular pharmaceutical carrier (See column 6, lines 60-67 bridging column 7, lines 1-10, in particular). The '478 patent teaches the reference agents is administered in multiple successive dosages, spaced as frequently as 6-12 hours apart or as long as six weeks until symptomatic relief is obtained (See column 7, lines 37-51, in particular). Claim 3 is included in this rejection because asthma induced airway hyperresponsiveness is due to inhalation or exposure to allergen. Claim 6 is included in this rejection because the references teach the reference agents are administered to ameliorate the symptoms associated with asthma. Claims 7 and 9 are included in this rejection because the '978 patent teaches administering CGRP to inhibit acute inflammation disorder such as asthma and the recitation of administering within 1 hour after the detection of the first symptoms of AHR or administered within 2 hours or less is within the purview of one skill in the art at the time the invention was made to intervene by administering CGRP as taught by the '978 and the '478 patents.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the CGRP as taught by the Nagase *et al* for the homolog of CGRP that binds to and activate CGRP receptor and in combination with another agent such as corticosteroids or phosphodiesterase inhibitor as taught by either the '978 patent or the '478 patent for a method of to inhibit allergen-induced airway hyperreponsiveness in a mammal as taught by Nagase *et al*. Hoshino *et al* and Elwood *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '978 patent teaches the CGRP and homologue thereof is useful for treating a variety of acute and chronic inflammatory respiratory disorders by administering CGRP alone and in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor conventionally used to treat chronic inflammatory respiratory disorders (See column 5, lines 36-39, lines 47-53, in particular). The '478 patent teaches the reference agents are useful in treatment of a variety of acute and chronic inflammatory respiratory disorders, by administering CGRP or homologue thereof alone or in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor which conventionally used to treat such diseases (See column 5, lines 36-39, lines 47-53, in particular). Nagase *et al* teach that CGRP pretreatment reduces HC induced airway hyperresponsiveness (AHR) in a mammal (See Fig 2, in

particular) and leukotriene (LTD1 induced airway constriction associated with asthma (See page 1555, column 2, first full paragraph, Fig 6, in particular). Hoshino *et al* teach that allergen induced bronchoconstriction in airway in guinea sensitized to allergen such as ovalbumin (OA) is accompanied by airway hyperresponsiveness and infiltration into the airway lumen of inflammatory cells such as eosinophils and neutrophils in bronchoalveolar lavage fluid (BALF) (See abstract, in particular). Elwood *et al* teach that bronchial hyperresponsiveness and increase in eosinophils counts in bronchoalveolar lavage fluid (BALF) of Brown-Norway rats sensitized to allergen such as ovalbumin that has many characteristics of human allergen-induced bronchial hyperresponsiveness (See abstract, in particular).

Applicants' arguments filed 1/29/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 1 has been amended. (2) The '978 and '478 patent teach the use of CGRP to ameliorate inflammatory conditions by inhibiting the release of proinflammatory cytokines such as IL-1 or IL-1 and IL-2. (3) Neither the '978 patent nor the '478 patent teach or suggest the use of CGRP to treat airway hyperresponsiveness. (4) Asthma is a lung disease that is typically characterized by periodic airflow limitation and/or hyperresponsiveness to a variety of stimuli such as exercise induced asthma, allergen induced asthma that results in excessive airway narrowing. (5) One could treat inflammation associated with asthma without treating airway hyperresponsiveness. (6) Even with the association between inflammation and allergen-induced AHR, the suggestion of the '978 patent to inhibit the release of IL-1 or IL-1 and IL-2 in a patient with allergen-induced AHR or any allergic inflammation including allergic asthma is not consistent with, and in fact is contrary to what is known about allergic inflammation by those of skill in the art.

In response to Applicants' argument that claim 1 has been amended to recite allergen induced airway hyperresponsiveness, Hoshino *et al* teach allergen induced bronchoconstriction in airway in guinea sensitized to allergen such as ovalbumin (OA) which is accompanied by airway hyperresponsiveness and infiltration into the airway lumen of inflammatory cells such as eosinophils and neutrophils in bronchoalveolar lavage fluid (BALF) (See abstract, in particular). Elwood *et al* teach that bronchial hyperresponsiveness and increase in eosinophils counts in bronchoalveolar lavage fluid (BALF) of Brown-Norway rats sensitized to allergen such as ovalbumin has many characteristics of human allergen-induced bronchial hyperresponsiveness (See abstract, in particular). Elwood *et al* teach allergen-induced bronchial responsiveness can be

measured by inhaled acetylcholine challenged and animals repeatedly exposed to allergen OV had an increased baseline lung resistance which is a significant increase in bronchial responsiveness to inhaled Ach (See abstract, in particular).

In response to Applicants' arguments in items 2-5 that neither the '978 patent nor the '478 patent teach or suggest the use of CGRP to treat airway hyperresponsiveness,

Nagase *et al* teach a method of inhibiting hyperpnea (dry air) induced airway hyperresponsiveness (AHR) in a mammal such as Guinea pig comprising administering to said Guinea pig an agent such as Calcitonin Gene-related peptide (CGRP) that binds to and activates a calcitonin gene related peptide receptor in the lungs (See page 1554, column 1, page 154, column 2, Effects of CGRP (8-37). The physiology of airway constriction or airway hyperresponsiveness (AHR) in hyperpnea induced AHR is equivalent to exercise induced asthma in humans (See page 1551, column 1, in particular) or allergen induced airway constriction associated with airway hyperresponsiveness (AHR) as taught by the Hoshino *et al.* Nagase et al teach that pretreatment with CGRP reduced HC induces airway hyperresponsiveness (AHR) in a mammal (See Fig 2, in particular). Nagase et al further teach pretreatment with CGRP reduces leukotriene (LTD1) induced constriction and LTD1 is associated with allergen-induced asthma (See page 1555, column 2, first full paragraph, Fig 6, in particular).

11. Claim 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase *et al* (of record, Am J Respir Crit Care Med 154: 1551-56, 1996; PTO 1449) in view of Hoshino et al (Arcugi 38(4): 314-25, 1989, Abstract, PTO 892) or Elwood et al (J Allergy Clin Immunol 88(6): 951-60, 1991; PTO 892) as applied to claims 1, 3-5, 8-9, 20, 23, 26, 29 and 38 mentioned above and further in view of Suissa *et al* (of record, Ann Intern Med 126(3): 177-83, Feb 1997; PTO 892).

The teachings of Nagase *et al*, Hoshino *et al* and Elwood *et al* have been discussed supra.

The claimed invention as recited in claim 25 differs from the combined teachings of the references only that the agent reduces the airway hyperresponsiveness of the mammal such that the FEV1 value of said mammal is improved by at least about 5%.

The claimed invention as recited in claim 27 differs from the combined teachings of the references only that the agent is a leukotriene modifiers such as receptor antagonist and β-agonists (along or short acting).

Suissa *et al* teach leukotriene receptor antagonist such as zafirluast and beta agonist treatment is more effective than beta-agonist alone in treating mild-to-moderate asthma (See abstract, in particular). Suissa *et al* teach patients with mild-to-moderate asthma, which have a decrease in forced expiratory volume in 1 s (FEV1) at least 55% of the predicted value and had demonstrated bronchial hyperresponsiveness, reduces airway hyperresponsiveness, zafirlukast alone improves bronchial hyperresponsiveness by 89%, which is at least 5% improvement (See entire document, abstract, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the leukotriene receptor antagonist or beta agonist as taught by Suissa *et al* with the Calcitonin Gene-related peptide (CGRP) as taught by Nagase *et al* for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal as taught by Nagase *et al*. Hoshino *et al* and Elwood *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Suissa *et al* teach any leukotriene receptor antagonist and beta agonist treatment is more effective than beta-agonist alone in treating mild-to-moderate asthma (See abstract, in particular) and zafirlukast alone improves bronchial hyperresponsiveness by 89%, which is at least 5% improvement (See entire document, abstract, in particular).

Applicants' arguments filed 1/29/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 1 has been amended. (2) Nagase et al does not teach or suggest a method of inhibit allergen induced airway hyperresponsiveness. (3) the combination of any or all the references with Suissa et al does not remedy the deficiencies of the primary references. (4) Nagase provides no motivation to treat allergen-induced AHR because results with hyperpnea induced AHR cannot be simply extrapolated to a type of AHR having a different etiology and pathophysiology. (5) The combination of Nagase and Suissa et al provide no expectation of success because one of skill in the art would not have an expectation that a result produced by hyperpnea-induced AHR shown by Nagase et al would necessarily be operable in the different condition of allergen-induced AHR. Suissa et al. is directed to the use of an entirely different compound for the treatment of asthma and therefore cannot contribute to any expectations with regard to CGRP.

In response to Applicants' arguments, Hoshino *et al* teach allergen induced bronchoconstriction in airway in guinea sensitized to allergen such as ovalbumin (OA) which is accompanied by airway hyperresponsiveness and infiltration into the airway lumen of inflammatory cells such as eosinophils and neutrophils in bronchoalveolar lavage fluid (BALF) (See abstract, in particular). Elwood *et al* teach that bronchial hyperresponsiveness and increase in eosinophils counts in bronchoalveolar lavage fluid (BALF) of Brown-Norway rats sensitized to allergen such as ovalbumin has many characteristics of human allergen-induced bronchial hyperresponsiveness (See abstract, in particular). Elwood *et al* teach allergen-induced bronchial responsiveness can be measured by inhaled acetylcholine challenged and animals repeatedly exposed to allergen OV had an increased baseline lung resistance which is a significant increase in bronchial responsiveness to inhaled Ach (See abstract, in particular). Nagase *et al* teach a method of inhibiting hyperpnea (dry air) induced airway hyperresponsiveness (AHR) in a mammal such as Guinea pig comprising administering to said Guinea pig an agent such as Calcitonin Gene-related peptide (CGRP) that binds to and activates a calcitonin gene related peptide receptor in the lungs (See page 1554, column 1, page 154, column 2, Effects of CGRP (8-37). The physiology of airway constriction or airway hyperresponsiveness (AHR) in hyperpnea induced AHR is equivalent to exercise induced asthma in humans (See page 1551, column 1, in particular) or allergen induced airway constriction associated with airway hyperresponsiveness (AHR) as taught by the Hoshino *et al*.

The combined teachings of the Nagase, Hoshino *et al* Elwood *et al* and Suissa et al provide expectation of success because one of skill in the art would have an expectation that CGRP would inhibit airway constriction or airway hyperresponsiveness (AHR) since airway constriction such as hyperpnea-induced AHR shown by Nagase et al is equivalent to airway constriction in allergen-induced AHR shown by Hoshino *et al* and Elwood *et al*. Suissa *et al* teach leukotriene receptor antagonist such as zafirluast and beta agonist treatment is more effective than beta-agonist alone in treating mild-to-moderate asthma (See abstract, in particular). Suissa *et al* teach patients with mild-to-moderate asthma, which have a decrease in forced expiratory volume in 1 s (FEV1) at least 55% of the predicted value and had demonstrated bronchial hyperresponsiveness, reduces airway hyperresponsiveness, zafirlukast alone improves bronchial hyperresponsiveness by 89%, which is at least 5% improvement (See entire document, abstract, in particular).

12. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase *et al* (of record, Am J Respir Crit Care Med 154: 1551-56, 1996; PTO 1449) in view of Hoshino *et al* (Areugi 38(4): 314-25, 1989, Abstract, PTO 892) or Elwood *et al* (J Allergy Clin Immunol 88(6): 951-60, 1991; PTO 892) as applied to claims 1, 3-5, 8-9, 20, 23, 26, 29 and 38 mentioned above and further in view of Drazen *et al* (of record, Am J Respir Crit Care Med 157(2): S233-7, June 1998; PTO 892) or Abraham *et al* (of record, Pulm Pharmacol 11(4): 271-6, June 1998; PTO 892) or Abdelaziz *et al* (Eur Respir J 10(4): 851-7; April 1997; PTO 892) or Barnes *et al* (of record, Eur Respir J 7(3): 579-91, March 1994; PTO 892) or Hoshino *et al* (of record, Allergy 52(8): 814-20, Aug 1997; PTO 892).

The teachings of Nagase *et al*, Hoshino *et al* and Elwood *et al* have been discussed supra.

The claimed invention as recited in claim 27 differs from the combined teachings of the references only that the method wherein the agent is administered to a mammal in conjunction with another agent selected from the group consisting of β-agonists, leukotriene modifiers (inhibitors or receptor antagonists), antihistamines, sodium cromoglycate, nedocrimal and theophylline.

Drazen *et al* teach leukotriene receptor antagonist such as (cysteinyl leukotriene (cysLT) and zafirlukast and 5-lipoxygenase (5-LO) inhibitor such as zileuton are safe and effective asthma treatment that improve pulmonary function and reduce airway inflammation, including inflammatory cell counts and airway hyperresponsiveness (See abstract, in particular).

Abraham *et al* teach agents such as cromolyn sodium (disodium cromoglycate) and beta 2 mimetic reproterol hydrochloride in combination gives better protection against post-antigen-induced airway hyperresponsiveness (AHR) than either one alone (See abstract, in particular).

Abdelaziz *et al* teach agent such as nedocromil sodium can reduce airway hyperresponsiveness by inhibiting eosinophil chemotaxis and adherence induced by human bronchial cell derived mediators (See abstract, in particular).

Barnes *et al* teach agent such as theophylline for treatment of asthma and is widely use as a bronchodilator and has anti-inflammatory activities such as inhibiting cytokines synthesis and release, and airway hyperresponsiveness (See abstract, in particular).

Hoshino *et al* teach an agent such as Ketotifen, which is an antihistamine, is beneficial for inhibiting activated eosinophils and T cell infiltration of inflammatory cells into the airway associated with asthma.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the leukotriene receptor antagonist and 5-lipoxygenase (5-LO) inhibitor as taught by Drazen *et al* or the cromolyn sodium as taught by Abraham *et al* or the nedocromil sodium as taught by Abdelaziz *et al* or the theophylline as taught by Barnes *et al* or the anti-histamine as taught by Hoshino *et al* with the Calcitonin Gene-related peptide (CGRP) as taught by Nagase *et al* for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal taught by Nagase *et al* Hoshino *et al* and Elwood *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Drazen *et al* teach any leukotriene receptor antagonist and any 5-lipoxygenase (5-LO) inhibitors are effective for asthma since it improves pulmonary function and reduces airway inflammation, including inflammatory cell counts and airway hyperresponsiveness (See abstract, in particular). Abraham *et al* teach cromolyn sodium (disodium cromoglycate) and beta 2 mimetic reproterol hydrochloride in combination gives better protection against post-antigen-induced airway hyperresponsiveness (AHR) than either one alone (See abstract, in particular). Abdelaziz *et al* teach nedocromil sodium can reduce airway hyperresponsiveness by inhibiting eosinophil chemotaxis and adherence induced by human bronchial cell derived mediators (See abstract, in particular). Barnes *et al* teach agent such as theophylline is useful as a bronchodilator and has anti-inflammatory activities such as inhibiting cytokines synthesis and release, including airway hyperresponsiveness (See abstract, in particular). Hoshino *et al* teach an agent any antihistamine, is beneficial for inhibiting activated eosinophils and T cell infiltration of inflammatory cells into the airway associated with asthma. Nagase *et al* teach Calcitonin Gene-related peptide (CGRP) is useful for inhibiting airway hyperresponsiveness (AHR) in a mammal.

Applicants' arguments filed 1/29/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) none of the references teaches or suggest a method of inhibit allergen-induced airway hyperresponsiveness by administering an animal an agent with CGRP as presently claimed. (2) The combination of references fails to provide any motivation to make the combination.

In response to Applicants' arguments, Hoshino *et al* teach that allergen induced bronchoconstriction in airway in guinea sensitized to allergen such as ovalbumin (OA) is

accompanied by airway hyperresponsiveness and infiltration into the airway lumen of inflammatory cells such as eosinophils and neutrophils in bronchoalveolar lavage fluid (BALF) (See abstract, in particular). Elwood *et al* teach that bronchial hyperresponsiveness and increase in eosinophils counts in bronchoalveolar lavage fluid (BALF) of Brown-Norway rats sensitized to allergen such as ovalbumin has many characteristics of human allergen-induced bronchial hyperresponsiveness (See abstract, in particular). Elwood *et al* further teach bronchial hyperresponsiveness and increase in eosinophils counts in bronchoalveolar lavage fluid (BALF) of Brown-Norway rats sensitized to allergen such as ovalbumin has many characteristics of human allergen-induced bronchial hyperresponsiveness (See abstract, in particular).

Nagase *et al* teach a method of inhibiting hyperpnea (dry air) induced airway hyperresponsiveness (AHR) in a mammal such as Guinea pig comprising administering to said Guinea pig an agent such as Calcitonin Gene-related peptide (CGRP) that binds to and activates a calcitonin gene related peptide receptor in the lungs (See page 1554, column 1, page 154, column 2, Effects of CGRP (8-37). The physiology of airway constriction or airway hyperresponsiveness (AHR) in hyperpnea induced AHR is equivalent to exercise induced asthma in humans (See page 1551, column 1, in particular) or allergen induced airway constriction associated with airway hyperresponsiveness (AHR) as taught by the Hoshino *et al.* Nagase et al teach that pretreatment with CGRP reduced HC induces airway hyperresponsiveness (AHR) in a mammal (See Fig 2, in particular). Nagase et al further teach pretreatment with CGRP reduces leukotriene (LTD1) induced constriction and LTD1 is associated with allergen-induced asthma (See page 1555, column 2, first full paragraph, Fig 6, in particular). The combined teachings of the references provide expectation of success because one of skill in the art would have an expectation that CGRP would inhibit airway constriction or airway hyperresponsiveness (AHR) since airway constriction such as hyperpnea-induced AHR shown by Nagase et al is equivalent to airway constriction in allergen-induced AHR shown by Hoshino *et al* and Elwood *et al.* Drazen *et al* teach any leukotriene receptor antagonist and any 5-lipoxygenase (5-LO) inhibitors are effective for asthma since it improves pulmonary function and reduces airway inflammation, including inflammatory cell counts and airway hyperresponsiveness (See abstract, in particular). Abraham *et al* teach cromolyn sodium (disodium cromoglycate) and beta 2 mimetic reproterol hydrochloride in combination gives better protection against post-antigen-induced airway hyperresponsiveness (AHR) than either one alone (See abstract, in particular). Abdelaziz *et al* teach nedocromil sodium can reduce airway hyperresponsiveness by inhibiting eosinophil

chemotaxis and adherence induced by human bronchial cell derived mediators (See abstract, in particular). Barnes *et al* teach agent such as theophylline is useful as a bronchodilator and has anti-inflammatory activities such as inhibiting cytokines synthesis and release, including airway hyperresponsiveness (See abstract, in particular). Hoshino *et al* teach an agent any antihistamine, is beneficial for inhibiting activated eosinophils and T cell infiltration of inflammatory cells into the airway associated with asthma. Nagase *et al* teach Calcitonin Gene-related peptide (CGRP) is useful for inhibiting airway hyperresponsiveness (AHR) in a mammal.

13. Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase *et al* (of record, Am J Respir Crit Care Med 154: 1551-56, 1996; PTO 1449) in view of Hoshino et al (Areugi 38(4): 314-25, 1989, Abstract, PTO 892) or Elwood et al (J Allergy Clin Immunol 88(6): 951-60, 1991; PTO 892) as applied to claims 1, 3-5, 8-9, 20, 23, 26, 29 and 38 mentioned above and further in view of Cadieux *et al* (of record, American J of Respiratory and Critical Care Medicine 159(1): 235-243, Jan 1999; PTO 1449).

The teachings of Nagase *et al*, Hoshino *et al* and Elwood *et al* have been discussed supra.

The claimed invention as recited in claim 12 differs from the combined teachings of the references only that the agent is administered at a dose of from about 0.1 μg/kg (0.1 μg x kilogram^{-1}) and about 20 μg per kg (0.1 μg x kilogram^{-1}) body weight of said animal.

The claimed invention as recited in claim 13 differs from the combined teachings of the references only that the agent is administered at a dose of from about 0.1 μg/kg (0.1 μg x kilogram^{-1}) and about 10 μg per kg (0.1 μg x kilogram^{-1}) body weight of said animal.

The claimed invention as recited in claim 14 differs from the combined teachings of the references only that the agent is administered at a dose of from about 0.1 μg/kg (0.1 μg x kilogram^{-1}) and about 20 μg per kg (0.1 μg x kilogram^{-1}) body weight of said animal.

Cadieux *et al* teach administering an agent such as CGRP at 0.38 to 114 μg/kg body weight which is about 20 μg/kg, causes a dose related inhibition of substance P induced bronchoconstriction and attenuate substance P induced bronchoconstriction in guinea pig presensitized to allergen such as ovalbumin (See Abstract, in particular). Cadieux *et al* teach CGRP acts as a potent broncoprotector agent on both guinea pig and human airway but its ability to limit the extent of airway responsiveness is strongly impaired in inflammatory conditions (Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the concentration in mg/kg body weight of CGRP as taught by the Nagase *et al* for the concentration in microgram per kg body weight as taught by Cadieux *et al* for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal as taught by Nagase *et al*. Hoshino *et al* and Elwood *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Cadieux *et al* teach administering an agent such as CGRP at 0.38 to 114 μg/kg body weight which is about 20 or 10 μg/kg, causes a dose related inhibition of substance P induced bronchoconstriction and attenuate substance P induced bronchoconstriction in guinea pig presensitized to allergen such as ovalbumin (See Abstract, in particular). The term "about" is open ended. It expands the claimed range to include the range taught by Cadieux *et al*. Claim 13 is included in this rejection because it is within the purview of one skill in the art at the time the invention was made to dilute the concentration and to administer an effective dose of CGRP for a method to inhibit allergen induced airway hyperresponsiveness in a mammal as taught by Nagase *et al*, Hoshino *et al* and Elwood *et al* and Cadieux *et al*.

Applicants' arguments filed 1/29/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) none of the references teaches or suggest a method of inhibit allergen-induced airway hyperresponsiveness by administering an animal an agent with CGRP as presently claimed. (2) Cadieu et al teach CGRP inhibits bronchoconstriction is not induced by allergen similar to Nagsse et al.

In response to Applicants' arguments, Hoshino *et al* teach that allergen induced bronchoconstriction in airway in guinea sensitized to allergen such as ovalbumin (OA) is accompanied by airway hyperresponsiveness and infiltration into the airway lumen of inflammatory cells such as eosinophils and neutrophils in bronchoalveolar lavage fluid (BALF) (See abstract, in particular). Elwood *et al* teach that bronchial hyperresponsiveness and increase in eosinophils counts in bronchoalveolar lavage fluid (BALF) of Brown-Norway rats sensitized to allergen such as ovalbumin has many characteristics of human allergen-induced bronchial hyperresponsiveness (See abstract, in particular). Elwood *et al* further teach bronchial hyperresponsiveness and increase in eosinophils counts in bronchoalveolar lavage fluid (BALF)

of Brown-Norway rats sensitized to allergen such as ovalbumin has many characteristics of human allergen-induced bronchial hyperresponsiveness (See abstract, in particular).

Nagase *et al* teach a method of inhibiting hyperpnea (dry air) induced airway hyperresponsiveness (AHR) in a mammal such as Guinea pig comprising administering to said Guinea pig an agent such as Calcitonin Gene-related peptide (CGRP) that binds to and activates a calcitonin gene related peptide receptor in the lungs (See page 1554, column 1, page 154, column 2, Effects of CGRP (8-37). The physiology of airway constriction or airway hyperresponsiveness (AHR) in hyperpnea induced AHR is equivalent to exercise induced asthma in humans (See page 1551, column 1, in particular) or allergen induced airway constriction associated with airway hyperresponsiveness (AHR) as taught by the Hoshino *et al.* Nagase et al teach that pretreatment with CGRP reduced HC induces airway hyperresponsiveness (AHR) in a mammal (See Fig 2, in particular). Nagase et al further teach pretreatment with CGRP reduces leukotriene (LTD1) induced constriction and LTD1 is associated with allergen-induced asthma (See page 1555, column 2, first full paragraph, Fig 6, in particular). The combined teachings of the references provide expectation of success because one of skill in the art would have an expectation that CGRP would inhibit airway constriction or airway hyperresponsiveness (AHR) since airway constriction such as hyperpnea-induced AHR shown by Nagase et al is equivalent to airway constriction in allergen-induced AHR shown by Hoshino *et al* and Elwood *et al.*

14. Claims 15, 28, 39 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase *et al* (of record, Am J Respir Crit Care Med 154: 1551-56, 1996; PTO 1449) in view of Hoshino et al (Areugi 38(4): 314-25, 1989, Abstract, PTO 892) or Elwood et al (J Allergy Clin Immunol 88(6): 951-60, 1991; PTO 892) as applied to claims 1, 3-5, 8-9, 20, 23, 26, 29 and 38 mentioned above and further in view of WO 98/03534 publication (January 1998; PTO 1449).

The teachings of Nagase *et al*, Hashino et al, and Elwood et al have been discussed supra.

The claimed invention as recited in claim 15 differs from the combined teachings of the references only that the agent is a product of rational drug design that binds to and activates a CGRP receptor.

The claimed invention as recited in claim 28 differs from the combined teachings of the references only that the agent is administered to said mammal in conjunction with a CGRP receptor activity modified protein (RAMP).

The claimed invention as recited in claim 39 differs from the combined teachings of the references only that the agent is a fragment of CGRP that binds to and activates a CGRP receptor.

The claimed invention as recited in claim 41 differs from the combined teachings of the references only that the agent is a CGRP analog that binds to and activates a CGRP receptor.

The WO 98/03543 publication teaches various calcitonin gene-related peptide agonist and antagonists such as CGRP-RCF analog and fragment thereof that binds to the CGRP receptor and retains essentially the same biological function as a human CGRP-polypeptide (See page 22, line 27, page 46, agonists and antagonists, in particular) for treating allergies (abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the Calcitonin Gene-related peptide (CGRP) as taught by Nagase *et al* for the Calcitonin Gene-related peptide (CGRP) agonist such as analog CGRP-RCF or peptide fragment thereof as taught by the WO 98/03543 for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal taught by Nagase *et al* Hoshino *et al* and Elwood *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 98/03543 publication teaches the reference CGRP analog is useful for treating asthma and allergies (See abstract, in particular).

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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April 21, 2003

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